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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/761,636	01/18/2001	Marc G. Achen	1064/48505	6112

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/761,636	ACHEN ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,12-18,23-26,49-63 and 72-103* is/are pending in the application.

4a) Of the above claim(s) *4,14-17,25,52,56-62 and 89-103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,12,13,18,23,24,26,49-55, 63 and 72-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/15/04 has been entered.

2. Claims 1-4, 12-18, 23-26, 49-63, and 72-103 are pending.

3. Claims 4, 14-17, 25, 52, 56-62 and 89-103 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-3, 12-13, 18, 23-24, 26, 49-55, 63, and 72-88 are being acted upon in this Office Action.

5. Claims 2-3, 13, 18, 50-55, and 63 are objected to because "A" should have been "The" for said dependent claims.

6. Claim 23 is objected to because said claim recites "a dimeric bicyclic peptide" which drawn to non-elected subject matter.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 12-13, 18, 23-24, 26, 49-55, 63, and 72-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a monocyclic peptide comprising a peptide sequence selected from the group consisting of SEQ ID NO: 5, 6, 7, 10, 11, 12, 13 and 14 as set forth in claims 49-55 for inhibiting VEGF-D induced VEGFR2 and VEGFR-3 mediated cell survival, **does not** reasonably provide enablement for (1) *any* monomeric monocyclic peptide as set forth in claims 1-3, 12-13, 18, 23-24, 26, 63, and 72-88 for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only monomeric monocyclic peptides derived from VEGF-D such as the ones shown in Table 1 on page 32 and Table 2 on page 47 of the specification. However, only three monocyclic peptides (peptides number 1-3), which correspond to SEQ ID NO: 5, 6, and 7, respectively, have been demonstrated to inhibit VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival. Note, none of the monocyclic peptides shown in Table 2 and dimeric bicyclic peptides shown in Table 3 were found to inhibit *any* VEGF, VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival. The specification further discloses that heterodimeric bicyclic peptide number 5, which corresponds to SEQ ID NO: 8 linked to SEQ ID NO: 9 (Table 1 on page 32) caused a significant reduction in cell number (Fig 11b). In contrast, neither homodimeric bicyclic peptides 4 and 6, which correspond to SEQ ID NO: 8 linked to SEQ ID NO: 8 or SEQ ID NO: 9 caused a significant change in cell number (page 39). None of the dimeric bicyclic peptides mentioned above appear to be more effective inhibitors than the monomeric monocyclic peptides in VEGF-D induced VEGFR-3 cell survival. The specification also discloses that deletion mutant selected from the group consisting of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution fail to inhibit the VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival.

The specification does not teach any monomeric monocyclic peptide as set forth in claims 1-3, 12-13, 18, 23-24, 26, 63, and 72-88 because there is insufficient guidance as to the structure associated with function of any monomeric monocyclic peptide without the amino acid sequence. There is insufficient guidance as to the structure of the "core sequence" of a receptor

binding loop 1, 2, or 3 of any VEGF such as VEGF, VEGF-C and VEGF-D, much less which amino acid within the undisclosed "core sequence" or "receptor binding loop" to be substitute, deleted, or inserted while which activity is retained or interferes by which receptor. In addition to the lack of enablement for "core sequence" mentioned above, the term "comprising" is open-ended. It expands the undisclosed "core sequence" having one or more amino acid substitution, or one or more amino acids deletion or insertion to include additional amino acids at either or both ends. There is no guidance as to which undisclosed amino acids to be added. Given the indefinite number of monomeric monocyclic peptide, there is insufficient working example demonstrating all monomeric monocyclic peptide interferes with all biological activity of VEGF, VEGF-C and VEGF-D mediated by VEGFR-2 or VEGFR-3. In the absence guidance as to the structure of the peptide, it is unpredictable which undisclosed monomeric monocyclic peptide is effective for interfering all biological activity of all VEGF mediated by VEGF-R2 or VEGFR-3.

It has been known in the art that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) is not well understood and is not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction,1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.).

Walsh *et al* teach that none of the available secondary structure predictors is able to predict accurately the secondary structure, and are not useful guides to designing peptides, let alone tertiary structure of the cysteine knot growth factors which the VEGF is a member (See page 395, in particular).

Kiba *et al* teach that a single loop of VEGF-A is not enough to be biologically functional. A pair of loop 1 and 3 of VEGF0ENZ-7 or VEGF-A may be required to build up the receptor binding for VEGFR-2 while loop 2 exchanges has no effect (See page 13461, column 1, second paragraph, in particular). Kiba *et al* further teach that even exchanging a region of VEGFA such as loop-3 with that of PIGF (member of the cysteine knot family) resulted with significant reduction in VEGFR-2 binding. However, its activity in inducing vascular permeability was still functional depending upon which bioassay (See page 13461, column 1, second paragraph, in particular).

Stacker *et al* teach that substituting amino acids 83-89 of VEGF with the analogous region of the related placenta growth factor (another member of the cysteine knot family) resulted in reduced VEGFR2 binding but retains the ability to induce vascular permeability using the Miles assay (See abstract, in particular).

Baldwin *et al* teach that receptor binding by VEGF-D is different in mouse and man (See entire document, abstract, in particular).

Attwood *et al*, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al*, of record, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. In fact, Table 2 of the specification shows that not all monomeric monocyclic peptides are created equal and demonstrate to have the desired inhibitory activity. Even if the monomeric monocyclic peptides limited to those shown in Table 2, there is no in vivo working example in the specification as filed to support that any monomeric monocyclic peptides mentioned above would inhibit the VEGF meditated cell growth (survival) for treating any disease. A pharmaceutical composition in the absence of in vivo data are unpredictable for the following reasons: (1) the monomeric monocyclic peptide may be inactivated before producing an effect, i.e. such as proteolytic degradation or short half-lives; (2) the monomeric monocyclic peptide may not reach the target area because, i.e. the monomeric monocyclic peptide may not be able to stay long enough in circulation due to clearance or simply has no effect; and (3) other functional properties, known or unknown, may make the monomeric monocyclic peptide unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Since the monomeric monocyclic peptides are not enabled, it follows that the composition comprising the undisclosed monomeric monocyclic peptides and a pharmaceutical carrier or adjuvant are not enabled. It also follows that any monomeric monocyclic peptide wherein the constraint maintains a beta-beta carbon separation distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom is not enable because the term "comprises" is open-ended. There is insufficient guidance as how to maintain distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom having additional undisclosed amino acids residues. With regard to claim 73, term "comprises" is open-ended. It expands the linking group to include additional carbon atoms at either or both ends to infinity, let alone the linking

group having extra undisclosed heteroatoms, straight chain, branched and containing one or more of any saturated, unsaturated or aromatic ring. Since any undisclosed monomeric monocyclic peptide mentioned above are not enabled, it follows that any monomeric monocyclic peptide wherein the hetero atom such as the ones recited in claim 74, any constraint such as the ones recited in claims 75-82, 84 and 88 are not enabled. It also follows any residues contributing to any said chains of any undisclosed monomeric monocyclic peptide mentioned above such as the ones recited in claims 83 and 85 are not enabled.

With regard to claims 49-55, the term "comprising" is open-ended. It expands the cyclic peptide to include additional amino acids at either or both ends to include the full length VEGF-D. Further, there is insufficient guidance as to which undisclosed amino acids to be included and the resulting monocyclic peptide interferes with VEGF-D from binding to the VEGF receptors. Given the indefinite number of undisclosed amino acids to be added, it is unpredictable which undisclosed monocyclic peptide would have the same function as the disclosed peptide of SEQ ID NO: 5-7, 10-14, in turn, would be useful for interfering a biological activity mediated by at least one of the receptor such as VEGF-R2 and VEGF-R3.

For these reasons, it would require undue experimentation for one even skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/15/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) it is routine experimentation to arrive at the claimed monocyclic peptides and to test whether they have the requisite biological activity. (2) Rather than all of the claimed peptides, the working examples are based on the loop fragments of the growth factors VEGF, VEGF-C, or VEGF-D. Because the loops are known to have a small number of residues, only a very limited amount of screening would be required to identify those

that when cyclized, maintain its affinity with one of VEGFs. (3) No undue experimentation is required and no in vivo data is required for the claimed invention.

In response, the specification does not define the "core sequence" of loop 1, loop 2, loop 3 of either VEGF, VEGF-C or VEGF-D, let alone which loop binds to which VEGF receptor. Further, there is insufficient guidance as to which amino acid within the undisclosed "core sequence" or "receptor binding loop" to be substitute, deleted, or inserted while which activity is retained or interferes by which receptor. In addition to the lack of enablement for "core sequence" mentioned above, the term "comprising" is open-ended. It expands the undisclosed "core sequence" having one or more amino acid substitution, or one or more amino acids deletion or insertion to include additional amino acids at either or both ends. There is no guidance as to which undisclosed amino acids to be added. Given the indefinite number of monomeric monocyclic peptide, there is insufficient working example demonstrating all monomeric monocyclic peptide interferes with all biological activity of VEGF, VEGF-C and VEGF-D mediated by VEGFR-2 or VEGFR-3. In the absence guidance as to the structure of the peptide, it is unpredictable which undisclosed monomeric monocyclic peptide is effective for interfering all biological activity of all VEGF mediated by VEGF-R2 or VEGFR-3. Applicant is directed to the detail explanation above.

9. Claims 1-3, 12-13, 18, 23-24, 26, 49-55, 63 and 72-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* monomeric monocyclic peptide as set forth in claims 1-3, 12-13, 18, 23-24, 26, 63 and 72-88 for treating *any* disease.

The specification discloses only monomeric monocyclic peptides derived from VEGF-D such as the ones shown in Table 1 on page 32 and Table 2 on page 47 of the specification. However, only three monocyclic peptides (peptides number 1-3), which correspond to SEQ ID NO: 5, 6, and 7, respectively, have been demonstrated to inhibit VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival. Note, none of the monocyclic peptides shown in Table 2 and dimeric bicyclic peptides shown in Table 3 were found to inhibit *any* VEGF, VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164

induced VEGFR-2 and VEGFR-3 mediated cell survival. The specification further discloses that heterodimeric bicyclic peptide number 5, which corresponds to SEQ ID NO: 8 linked to SEQ ID NO: 9 (Table 1 on page 32) caused a significant reduction in cell number (Fig 11b). In contrast, neither homodimeric bicyclic peptides 4 and 6, which correspond to SEQ ID NO: 8 linked to SEQ ID NO: 8 or SEQ ID NO: 9 caused a significant change in cell number (page 39). None of the dimeric bicyclic peptides mentioned above appear to be more effective inhibitors than the monomeric monocyclic peptides in VEGF-D induced VEGFR-3 cell survival. The specification also discloses that deletion mutant selected from the group consisting of SEQ ID NO: 10, 11 and 12 having one or two internal amino acid deletion or amino acid substitution fail to inhibit the VEGF-DΔNΔC, VEGF-C, VEGF-D and mouse VEGF164 induced VEGFR-2 and VEGFR-3 mediated cell survival.

Other than the specific monocyclic peptide comprising a peptide sequence selected from the group consisting of SEQ ID NO: 5, 6, 7, 10, 11, 12, 13 and 14 as set forth in claims 49-55 for inhibiting VEGF-D induced VEGFR2 and VEGFR-3 mediated cell survival, there is inadequate written description about the structure associated with function of *any* "core sequence", *any* "receptor binding loop 1, 2, or 3" of any VEGF such as VEGF, VEGF-C and VEGF-D. Further, there is inadequate written description about which amino acid within the undisclosed "core sequence" or "receptor binding loop 1, 2 or 3" to be substitute, deleted, or inserted while which activity is retained or interferes by which receptor. In addition to the lack of a written description for "core sequence" mentioned above, the term "comprising" is open-ended. It expands the undisclosed "core sequence" having one or more amino acid substitution, or one or more amino acids deletion or insertion to include additional amino acids at either or both ends. There is insufficient written description about undisclosed amino acids to be added and retains the desired activity mediated by the specific VEGF receptor. Given the indefinite number of undisclosed monomeric monocyclic peptide, it follows that the amino acids within the loops or core sequence mentioned above comprising the extra undisclosed amino acid residues to be substitute, delete and/or add are not adequately described. It also follows that any composition comprising any undisclosed monomeric monocyclic peptides are not adequately described. Because the primary structure of the core sequence has not been described, the tertiary structure of any monomeric monocyclic peptide wherein the constraint maintains a beta-beta carbon separation distinct between opposing anti-parallel strands of any loop or any loop fragment at less than 6 angstrom is not adequately described. Further, the term "comprises" is open-ended. It expands the linking

group to include additional atoms, or heteroatoms (claim 73) to include additional amino acid residues or carbon atoms at either or both ends. There is a lack of written description about which undisclosed atoms or amino acids to be included while maintains VEGF receptors binding and interferes with all its biological activity.

With regard to claims 49-55, the term "comprising" is open-ended. It expands the cyclic peptide to include additional amino acids at either or both ends to include the full length VEGF-D. Further, there is inadequate written description about which undisclosed amino acids to be included and whether the resulting monocyclic peptide interferes with VEGF-D from binding to the VEGF receptors. Given the indefinite number of undisclosed amino acids to be added, the monocyclic peptide as set forth in claims 49-55 is not adequately described, let alone it interferes with a biological activity mediated by at least one of the receptor such as VEGF-R2 and VEGF-R3. Since any of the undisclosed monomeric monocyclic peptide mentioned above are not adequately described, it follows that any monomeric monocyclic peptide wherein the hetero atom such as the ones recited in claim 74, any constraint such as the ones recited in claims 75-82, 84 and 88 are not adequately described. It also follows any residues contributing to any said chains of any undisclosed monomeric monocyclic peptide mentioned above such as the ones recited in claims 83 and 85 are not adequately described. It also follows that any composition comprising the undisclosed monomeric monocyclic peptide are not adequately described.

The specification discloses only various monomeric monocyclic peptides derived from only human VEGF-D, the other monomeric monocyclic peptide derived from VEGF-C or VEGF are not adequately described. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species functional monomeric monocyclic peptide to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/15/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 has been amended. (2) the specification describes how variants of the specifically disclosed core sequences can be obtained by an ordinary skill persons, and guidelines as to which specific amino acid residue of the polypeptide are conserved

for maintaining a receptor binding activity. (3) the claimed genus is not highly variable in view of the fact that the loop sequences are relatively short, well characterized and have highly conserved structural and functional characteristics.

In response to Applicant's arguments, , there is inadequate written description about the structure associated with function of any "core sequence", any receptor binding loop 1, 2, or 3 of any VEGF such as VEGF, VEGF-C and VEGF-D. Further, there is inadequate written description about which amino acid within the undisclosed "core sequence" or "receptor binding loop 1, 2 or 3" to be substitute, deleted, or inserted while which activity is retained or interferes by which receptor. In addition to the lack of a written description for "core sequence" mentioned above, the term "comprising" is open-ended. It expands the undisclosed "core sequence" having one or more amino acid substitution, or one or more amino acids deletion or insertion to include additional amino acids at either or both ends. There is insufficient written description about undisclosed amino acids to be added and retains the desired activity mediated by the specific VEGF receptor. Given the indefinite number of undisclosed monomeric monocyclic peptide, it follows that the amino acids within the loops or core sequence mentioned above comprising the extra undisclosed amino acid residues to be substitute, delete and/or add are not adequately described. It also follows that any composition comprising any undisclosed monomeric monocyclic peptides are not adequately described. The specification discloses only various monomeric monocyclic peptides derived from only human VEGF-D, the other monomeric monocyclic peptide derived from VEGF-C or VEGF are not adequately described. Applicant is directed to the explanation discussed supra.

10. Claims 1-3, 12-13, 18, 23-24, 26, 63 and 72-88 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The monomeric monocyclic peptide ...comprises (1) "a core sequence which consists of a receptor-binding loop 1, 2 or 3 of VEGF, VEGF-C"...or VEGF-D in Claim 1 and dependent claims therefrom represents a departure from the specification and the claims as originally filed because said phrase has no support in the claims and the specification as originally filed. The specification discloses a monomeric monocyclic peptide inhibitor based on loop 1, 2 or 3 of **VEGF-D** (See on page 13 at line 27). Further, Applicants have not pointed out the support for

said phrase. Further, the "first linking group at one end of the core sequence and a second linking group at the other end of the core sequence wherein the first and second linking groups are connected to form a constraint that cyclizes the peptide such that receptor-binding loop 1, 2 or 3 or the corresponding loop fragment mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D" in claims 1 and dependent claims thereof represents a departure from the specification and the claims as originally filed because said phrase has no support in the specification and the claims as originally filed. The "further comprises deleting at least one amino acid from said loop fragment prior to cyclizing the peptide" in claim 18 has no support in the specification or the claims as originally filed. Applicants have not pointed out the support for said phrase.

"A monomeric, monocyclic peptide produced by a method comprising: obtaining "a receptor-binding loop 1, 2, and 3 of VEGF, VEGFC *and* VEGF-D"..in claim 12 represents a departure from the specification and the claims as originally filed because said phrase has no support in the claims and the specification as originally filed. The specification discloses a monomeric monocyclic peptide inhibitor based on loop 1, 2 or 3 of **VEGF-D** (See on page 13 at line 27). Further, Applicants have not pointed out the support for said phrase.

Applicants' arguments filed 1/15/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) example 1 of the specification makes apparent that the 3-D structure is known and from this 3-D structure the loops of VEGF are apparent by visual inspection. It is well known that all members of the VEGF family of cysteine knot proteins have loops 1, 2 and 3.

In response, the specification discloses a monomeric monocyclic peptide inhibitor based on loop 1, 2 or 3 of **VEGF-D** (See on page 13 at line 27). Although the specification states that each VEGF family member has between 30% and 45% amino acid sequence identity with VEGF; the VEGF family members share a VEGF homology domain which contains the six cysteine residues which form the cysteine-knot motif", the specification does not disclosed the specific "core sequence" of each VEGF member such as VEGF-C, VEGF-D, and VEGF given that each has only 30 and 45% sequence identity. Further, there is a lack of written description about which amino acid sequence represents the loop 1, 2 and loop 3 of VEGF-C, loop 1, 2 and 3 of VEGF-D and loop 1, 2 and 3 of VEGF.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

12. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.
Patent Examiner
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March 22, 2004

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SUPERVISORY PATENT EXAMINER
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